Editorial

STAT3: a crucial target for ovarian cancer stem cells that inhibits WNT signaling through a novel epigenetic mechanism

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Ovarian cancer is the most lethal cause of death from gynecological malignancies (1). Most patients are diagnosed with advanced stage of metastatic disease (1). Following surgery and the standard chemotherapy, most patients gain initial complete response (2). However, the majority will eventually have a relapse and die of their disease (2). The overall survival rate remains poor, with the five-year survival rate below 25% for stage III–IV disease (1). Therefore, new regimens targeting the pathways involved in metastasis and chemoresistance is essential to the development of more effective therapies in ovarian cancer.

The metastatic pattern of ovarian cancer differs from that of most other epithelial cancers which are mainly mediated by dissemination through blood vessels and lymphatic vessels. However, ovarian cancer metastases primarily occur when cancer cells detach from the primary tumor site and disseminate throughout the peritoneal cavity (3). The disseminated cells form multicellular spheroids that either remain unattached or implant onto organs within the peritoneal cavity (3). It has become apparent that these multicellular spheroids contained within malignant ascites are a major source of disease recurrence and significantly impede efficacious treatment of advanced ovarian cancer (4).

The growth and maintenance of the spheroids is considered to be due to adhesive molecules that mediate cell-cell and cell-extracellular matrix (ECM) interactions (5). The expression of these adhesion molecules are mainly regulated by epithelial-mesenchymal transition (EMT) and EMT gene expression signatures are shown to be correlated with worse clinical outcomes (6,7). Cancer stem cells (CSCs), which has the capacity for extensive proliferation, self-renewal and high tumorigenic potential, have been found in most types of solid and hematopoietic tumors including ovarian cancer. Both EMT and CSCs play critical roles in cancer metastasis and therapeutic resistance, and there is a strong association between EMT-associated gene expression and CSCs (8).

Deregulation of canonical WNT/β-catenin signaling contributes to CSC populations, chemoresistance and the aggressiveness of ovarian cancer (9). WNT signaling comprises a canonical and a non-canonical arm, and the former relies directly on the transcription cofactor β-catenin (10). In the absence of WNT ligands, a multiprotein "destruction complex" phosphorylates β-catenin thereby targeting it for proteasomal degradation. When WNT ligands bind to and activate their receptors, formation of the destruction complex is inhibited. Consequently β-catenin is not phosphorylated and non-phosphorylated β-catenin translocates into the nucleus. In the nucleus it binds to the TCF/LEF family-transcription factors to activate gene expression. The WNT/β-catenin signaling pathway was shown to regulate EMT during embryogenesis. Key regulators of EMT such as various transcription factors are up-regulated by WNT/β-catenin signaling. Activation of WNT/β-catenin signaling is linked to initiation of EMT in ovarian cancer cells (9). Thus inhibiting WNT/β-catenin signaling could block both CSC and EMT pathways, which may lead to overcome chemoresistance in ovarian cancer.

Multicellular spheroids in ascites serve as the means for ovarian cancer metastases and represent a key barrier in the efficacy of chemotherapy agents. It was shown that

STAT3 was significantly enriched in the ascites of recurrent ovarian cancer patients (11). In addition, targeting STAT3 signaling results in the disruption of CSC maintenance and dramatically reduces the metastases and chemoresistance in ovarian cancer (12). Chen *et al*. recently demonstrated that targeting STAT3 signaling leads to the inhibition of WNT/β-catenin signaling, which effectively eliminates the formation of the metastatic niche and suppresses its persistence after chemotherapy in ovarian cancer (13). They showed that STAT3 can activate WNT signaling through the epigenetic inactivation of the WNT antagonist DKK1. Epigenetic silencing of DKK1 expression was previously shown to be linked to DNA hypermethylation, histone deacetylation and histone methylation (14). In this report (13), they demonstrated a novel mechanism by which STAT3 mediates DKK1 silencing; (I) STAT3 directly binds to the specific sites in the miR-92a promoter region and the promoter activity was decreased after the mutation of putative STAT3-binding sites, indicating that STAT3 is required for the transcriptional induction of miR-92a; (II) miR-92a negatively regulates protein levels of DKK1 by targeting a specific binding site in the DKK1 3' untranslated regions (UTRs) sequence. Their data were consistent with previous reports that the miR-17-92 cluster targets the E2F1 and HIPK1 proteins, which suppress WNT/β-catenin signaling (15) and that the miR-17-92 cluster was highly induced during early reprogramming stages in induced pluripotent stem cells (16).

Epigenetic regulators of tumor suppressors, including DNA methylation, histone modification and miRNAs play a prominent role in cancer recurrence (17-20). miRNAs are short (~22 nucleotide), untranslated RNAs that mediate post-transcriptional gene repression. Translated individually or as part of introns, miRNAs undergo a complex maturation process that results in their incorporation into an RNA induced silencing complex (RISC). The mature miRNA then induces post-transcriptional gene silencing by tethering RISCs to partly complementary sequence motifs in target mRNAs, predominantly found within the 3' UTRs. miRNAs have been gaining a prominent role in tumorigenesis since their discovery 20 years ago. Over-expressed miRNAs may function as oncogenes by down-regulating tumor suppressors (oncogenic miRNAs), whereas down-regulated miRNAs may act as tumor suppressors by negatively regulating oncogenes (onco-suppressor miRNAs). Several groups have identified miRNAs in ovarian cancer and correlated their expression to cancer recurrence and prognosis (17-19). Chen *et al*. demonstrates the ability of miR-92a to mediate STAT3-regulated self-renewal of ovarian CSCs, which suggests that miR-92a could also be a crucial therapeutic target in ovarian cancer (13).

As described, finding a new target for WNT signaling can contribute to the CSC- and EMT-targeted therapeutic strategy. Chen *et al*. has identified that STAT3 is enriched in ovarian CSCs, targets miR-92a/DKK1 and subsequently activates WNT/β-catenin signaling. They also demonstrated that targeting STAT3 in combination with paclitaxel treatment synergistically reduced peritoneal seeding and prolonged survival in a murine model of intraperitoneal ovarian cancer (13). These findings are of interest because recurrence after initial response is a main cause of mortality in advanced ovarian cancer. Based on these findings, it is therefore reasonable to propose that ovarian CSC-targeted therapy, such as STAT3 inhibition, in combination with the current standard chemotherapy may be a rational strategy for improving ovarian cancer patient survival.

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Footnote

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appropriately investigated and resolved.

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